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ORIGINAL ARTICLE

Rapid initiation of quetiapine well tolerated as compared with the conventional initiation regimen in patients with schizophrenia or schizoaffective disorders

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Abstract A 2-week, randomized, parallel-group open trial was designed to evaluate the safety and tolerability of a rapid initiation regimen with a higher dose of quetiapine (up to 800 mg/d by Day 4) than that used in the conventional initiation regimen of quetiapine (up to 400 mg/d by Day 5) in patients with schizophrenia or schizoaffective disorders. Forty patients were recruited and randomly (3:1) assigned to either the group with rapid initiation of quetiapine or the group with conventional initiation. At the end of the investigation, the difference between the groups in the incidence of adverse events was not significant; a significant drop in the Barnes Akathisia Rating Scale and Simpson-Angus Scale scores was observed only in the group with the rapid initiation regimen. The groups did not differ in terms of improvement on the Clinical Global Impression—Severity of Illness and Positive and Negative Syndrome Scale at the end of the study. The results of our 2-week study suggest that rapid initiation with a higher dose of quetiapine (up to 800 mg/d by Day 4) is well tolerated in patients with schizophrenia or schizoaffective disorders and does not compromise efficacy relative to the conventional initiation.
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Introduction

Quetiapine is a dibenzothiazepine derivative that is used to treat patients with acute and chronic psychoses, such as schizophrenia [1]. The initiation regimen that is recommended in the prescribing information for quetiapine and approved by the regulatory authorities is a 4-day schedule that involves an initial dose of 50 mg on Day 1, increasing to 300 mg on Day 4 [2]. However, this schedule may be inappropriate for acutely ill patients who frequently require higher doses of quetiapine and rapid initiation of therapy [3]. If the initiation period of quetiapine could safely be reduced, acutely ill patients could receive higher doses within a shorter period than that in current clinical practice. The results of a recent pilot trial suggest that rapid initiation with a higher dose of quetiapine (400 mg/d by Day 2) is as safe as the approved initiation schedule and does not increase adverse effects or vital signs [4].

This study was designed as a pilot trial to determine whether a rapid dose initiation regimen with a high dose of quetiapine is safe and well tolerated in patients with acute schizophrenia or schizoaffective disorders. The objective of the trial was to evaluate the safety and tolerability of an initiation schedule that enables acutely ill patients to receive a dose of up to 800 mg/d of quetiapine by Day 4 (by comparison with the conventional dose initiation schedule, in which a dose of 300 mg/d is reached by Day 4). The Institutional Review Board of Chang Gung Memorial Hospital approved the study.

Materials and methods

Subject

Patients who were admitted to acute psychiatric wards with an acute exacerbation of schizophrenia or schizoaffective disorder and a Clinical Global Impression—Severity of Illness (CGI-S) score greater than or equal to 4 were enrolled in the study. The dose of previous oral antipsychotics was reduced as soon as possible after the initiation of the quetiapine treatment. Previously administered antipsychotics were withdrawn completely by Day 3 at the latest in all cases. From Day 3 onwards, no antipsychotic medication other than quetiapine was administered. Any contraindicated medication, as specified in the country-specific prescribing information, was prohibited. Psychotropic medications, including antidepressants and mood stabilizers, which were taken by the patient at stable doses for at least 4 weeks before entry into the trial, were continued. The introduction of any other psychotropic medication during the trial was prohibited. Patients were excluded if they had been treated with any depot antipsychotic medication within 1-day dosing interval before being excluded.

Study design

This study was a randomized, parallel-group open trial of two initiation regimens of quetiapine (rapid *vs*. conventional). An open-label design was regarded as sufficient because the primary objective was safety. Randomization eliminated any selection bias in the assignment of individuals to the study and control groups. The rapid dose initiation of quetiapine was compared with the conventional, recommended, and approved dose initiation of quetiapine. Using quetiapine for both groups made dose initiation the only difference between the two treatment groups. The total study period for each patient was 14 days. Patients were randomly assigned to rapid or conventional initiation groups in a ratio of 3:1. No violence or other emergent condition was observed in any patient in the rapid initiation group. The initial dose of quetiapine in the rapid initiation group was 200 mg once daily with increments of 100 mg twice a day thus reaching a dose of 800 mg on Day 4. A flexible dosing schedule of 400—800 mg/d from Day 5 to Day 14 was then applied. A flexible dosing schedule of 400—800 mg/d from Day 6 to Day 14 was then followed.

Assessments

Safety and tolerability

The following safety-related variables were measured: heart rate and blood pressure, including sitting diastolic blood pressure, standing diastolic blood pressure, sitting systolic blood pressure, and standing systolic blood pressure. All were measured within 1 hour of administration of each dose of quetiapine for the first 7 days and on Day 14 or during the last visit. Electrocardiography was conducted during the screening visit (Day 0) and on Day 14 or during the last visit. Extrapyramidal symptoms (EPSs) were also recorded using the Barnes Akathisia Rating Scale (BARS), the Simpson-Angus Scale (SAS), and by observation of any adverse events once a day for the first 7 days and on Day 14 or during the last visit [5,6]. All patients were examined by psychiatrists.

Efficacy

Drug efficacy was assessed using the CGI-S Scale and the Positive and Negative Syndrome Scale (PANSS) on Day 0 (screening), Day 1 (baseline), Day 5, Day 7, and Day 14 [7].

Statistical analysis

All data that were collected in the study were summarized for each treatment group using tables, graphs, and summary statistics. The data that were collected during Week 1 specifically targeted the analysis of safety and tolerability. The differences between the treatment groups in terms of efficacy were estimated by analysis of covariance, with the baseline score and treatment group assignment as covariables. For dropouts, the last observation was carried forward. Continuous variables were compared using Student t test or a paired-sample t test and correlated using partial correlation. Categorical variables were compared using the Chi-square test. A two-tailed p value less than 0.05 was regarded as statistically significant.

Results

Baseline characteristics

A total of 40 patients were screened, and all were found to be eligible for participation in the study. Patients in the

Table 1 Baseline characteristics of all randomized patients

Characteristics	Rapid initiation ($n = 30$)	Conventional initiation ($n = 10$)
	Mean ± SD	Mean ± SD
Height (cm)	164.7 ± 8.3	160.6 ± 8.7
Weight (kg)	66.2 ± 12.9	62.9 ± 11.9
Body mass index (kg/m^2)	24.5 ± 4.8	24.2 ± 3.0
Sitting systolic blood pressure (mmHg)	115.3 ± 15.7	114.7 ± 11.6
Standing systolic blood pressure (mmHg)	111.9 ± 13.6	114.4 ± 11.5
Sitting diastolic blood pressure (mmHg)	72.9 ± 10.6	70.2 ± 8.3
Standing diastolic blood pressure (mmHg)	73.4 ± 11.5	73.1 ± 7.7
Heart rate* (beats/min)	87.1 ± 16.3	75.0 ± 14.9
Barnes Akathisia Rating Scale	2.1 ± 3.1	0.9 ± 1.7
Simpson-Angus Scale	3.2 ± 3.6	2.1 ± 2.4
Clinical Global Impression—Severity of Illness	5.1 ± 0.9	5.0 ± 1.1
PANSS total score	87.6 ± 14.4	87.0 ± 14.7
PANSS positive score	23.4 ± 4.8	24.0 ± 4.8
PANSS negative score	20.9 ± 5.7	18.8 ± 4.2

*Statistically significant ($p < 0.05$).
PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

rapid initiation group ($n = 30$) were aged from 22 years to 57 years (mean ± standard deviation, 38.3 ± 10.1) and included 12 women (40%). Patients in the conventional initiation group were aged from 29 years to 58 years (mean, 42.7 ± 9.7) and included six women (60%). Table 1 presents the baseline characteristics of all 40 randomly assigned patients. No significant differences were found in patient characteristics or baseline parameters, except for the heart rate ($p = 0.045$). A significant difference in the quetiapine dose at Day 14 existed between the rapid initiation group (696.9 ± 174.2 mg/d) and the conventional initiation group (515.0 ± 305.6 mg/d) ($p = 0.026$).

Concomitant medications

The most common classes of drugs that were permitted by the protocol, if the patients had received stable doses for at least 4 weeks before entry into the study, and were, therefore, taken throughout the study, were sedatives, laxatives, and psychotropic medications.

Safety and tolerability

Four patients (13%) in the rapid initiation group did not complete the study because of hypersomnia in one patient and worsening of the underlying condition in three patients. Three patients (30%) in the conventional initiation group did not complete the study because of worsening of the underlying condition in one patient and withdrawal of consent by two patients.

The primary endpoints were dropouts attributed to adverse events and the total number of adverse events reported by the end of Week 1. Only one patient in the rapid initiation group dropped out because of an adverse event (hypersomnia), and the investigator judged this event to be treatment related. Table 2 summarizes the adverse events, all of which occurred with an incidence greater than 5% during Week 1. In the rapid initiation group, the most frequently reported adverse event was constipation [12 patients (40%)]. The difference between the incidences of adverse events in the groups during Week 1 was not significant, except in the case of constipation ($p = 0.019$). The incidence of extrapyramidal adverse events that are commonly associated with antipsychotics, such as gait disturbance, akathisia, and tremor, did not differ significantly between the two groups. In the first week, 18 patients (60%) in the rapid initiation group and five patients (50%) in the conventional initiation group reported treatment-related adverse events, indicating statistical difference between the groups ($p = 0.154$). The between-group differences in sitting diastolic blood pressure, standing diastolic blood pressure, sitting systolic blood pressure, and standing systolic blood pressure were not significant at any time during the study.

The baseline heart rates that were measured while the patients were seated differed significantly between the rapid and conventional initiation groups ($p = 0.045$). The change in the heart rate from the baseline was not

Table 2 Summary of adverse events reported during the first week of treatment

Adverse event	Rapid initiation ($n = 30$)	Conventional initiation ($n = 10$)	p
	n (%)	n (%)	
Gastrointestinal disorders			
Constipation	12 (40)	0 (0.0)	0.019*
Nervous system disorders			
Gait disturbance	2 (6.7)	1 (10.0)	1.000
Akathisia	2 (6.7)	0 (0.0)	1.000
Dizziness	3 (10.0)	1 (10.0)	1.000
Somnolence	6 (20.0)	1 (10.0)	0.656

*Statistically significant ($p < 0.05$).

Table 3 Mean change in BARS and SAS scores from baseline to study end (LOCF)

Scale	Mean change from baseline (SD)		
	Day 5	Day 7	Day 14
BARS			
Rapid initiation ($n = 30$)	−1.37 (2.63)*	−1.54 (3.08)*	−1.73 (2.95)*
Conventional initiation ($n = 10$)	−0.63 (1.41)	−0.13 (0.35)	−0.30 (0.48)
SAS			
Rapid initiation ($n = 30$)	−2.00 (3.18)*	−2.69 (3.54)*	−2.60 (3.88)*
Conventional initiation ($n = 10$)	−1.50 (2.93)	−0.75 (3.06)	−0.90 (2.88)

*Scale score reduced significantly from baseline ($p < 0.05$).
BARS = Barnes Akathisia Rating Scale; SAS = Simpson-Angus Scale; SD = standard deviation.

significant in either group at any point in the study. The difference between the changes in the heart rates of the patients in the two groups from the baseline values was not significant at any visit. The shift from normal to abnormal electrocardiography and *vice versa* was not significant ($p = 1.00$ in the rapid initiation group and $p = 0.56$ in the conventional initiation group).

Incidence of adverse events (days 1−14)

Adverse events were reported by 93.3% of the patients in the rapid initiation group and by 80.0% of the patients in the conventional initiation group, but none of the reported adverse events was serious. The most frequently reported adverse event was constipation (43.3% in the rapid initiation group and 10.0% in the conventional initiation group).

In the rapid initiation group, the following adverse events were reported with a frequency greater than 10%: alteration of mood (23.3%), somnolence (20.0%), dizziness (16.7%), anxiety (13.3%), and hypersomnia (10%). In the conventional initiation group, the following adverse events were reported with a frequency greater than 10%: hypersomnia (30.0%), alteration of mood (20.0%), diarrhea (20.0%), somnolence (10.0%), gait disturbance (10.0%), dizziness (10.0%), aggression (10.0%), anxiety (10.0%), eczema (10.0%), and skin exfoliation (10.0%).

The incidence rates of expected adverse events, such as gait disturbance, akathisia, extrapyramidal syndrome, hypersomnia, and tremor did not differ significantly different the two groups. Treatment-related adverse events were observed in 20 patients (66.7%) in the rapid initiation group and in five patients (50%) in the conventional initiation group.

BARS and SAS

Table 3 shows that the rapid initiation group had significantly continuous decrease in the BARS and SAS scores from their baseline values on Day 5, Day 7, and Day 14. It is different between the two groups.

Efficacy

Table 4 shows that the rapid initiation group exhibited significant improvement in the mean PANSS negative score from the baseline value on Day 5, Day 7, and Day 14. Only the rapid initiation group maintained significant CGI-S score improvements and PANSS positive score improvements until the end of the study.

Discussion

This investigation compared the safety and tolerability of a rapid initiation regimen with a higher dose of quetiapine

Table 4 Mean change from baseline in CGI-S and PANSS scores at Day 5, Day 7, and Day 14 (LOCF)

Scale	Mean change from baseline (SD)		
	Day 5	Day 7	Day 14
CGI-S			
Rapid initiation ($n = 30$)	−0.73 (0.58)*	−1.13 (0.86)*	−1.50 (1.01)*
Conventional initiation ($n = 10$)	−0.70 (0.95)*	−0.80 (0.92)*	−0.80 (1.48)
PANSS positive score			
Rapid initiation ($n = 30$)	−3.40 (3.70)*	−4.77 (4.72)*	−6.37 (6.08)*
Conventional initiation ($n = 10$)	−4.20 (4.57)*	−4.90 (4.46)*	−4.30 (7.39)
PANSS negative score			
Rapid initiation ($n = 30$)	−2.57 (3.21)*	−3.97 (3.84)*	−5.47 (4.39)*
Conventional initiation ($n = 10$)	−0.80 (2.35)	−1.50 (2.76)	−2.30 (3.92)

*Scale score reduced significantly from baseline ($p < 0.05$).
CGI-S = Clinical Global Impression—Severity of Illness; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

than that conventionally used with those of the current conventional initiation regimen that is approved in Taiwan.

Numerous clinical investigations have supported the use of a rapid dose initiation regimen with a higher dose of quetiapine than that conventionally used [4,8—12]. Smith et al. [4] reported that patients for whom quetiapine was titrated to 400 mg/d by Day 2 had the same adverse events as patients who followed the usual 5-day initiation schedule. In a study of hospitalized patients with psychoses, doses of quetiapine up to 1,600 mg/d were effective and well tolerated, with no evidence of EPS [12]. Ganesan et al. [9] observed that, for patients with psychosis who exhibited aggression in an emergency setting, treatment with quetiapine at doses up to 1,000 mg/d reduced aggressive behavior, including aggression against others, by the second day of treatment. Together with results concerning safety, the data herein suggest that a rapid initiation regimen with a higher dose of quetiapine that is conventionally used is suitable in acute cases. Significant improvements in the mean CGI-S score, PANSS positive score, and PANSS negative score from their baselines were observed on Day 14 only for the rapid initiation group and not for the conventional initiation group.

In the present study, the incidence of adverse events during Week 1 was of particular interest because the outcome of the rapid initiation schedule was most evident during this period. The results of this study reveal that the incidence of adverse events, except constipation, did not differ significantly between the rapid and conventional initiation schedules. The incidence of constipation was significantly higher in the rapid initiation group during Week 1. Raedler et al. [13] found that treatment with higher doses of quetiapine was associated with constipation. *N*-desalkyl quetiapine, a metabolite of quetiapine, is an antagonist of the muscarinic 1, 3, and 5 receptors. The possible contribution of this metabolite to constipation has been discussed [14]. However, severe constipation did not cause any patient in the rapid initiation group to drop out.

Somnolence is regarded as a common side effect of quetiapine treatment, but no evidence suggests that the conventional initiation schedule reduces the incidence of somnolence compared with the rapid initiation schedule [15,16]. A previous study of rapid dose titration with high doses of quetiapine for treating acute psychotic cases revealed that the most common adverse event was sedation. In another such study, however, only one patient experienced transient somnolence [17,18]. In the present study, the incidence of somnolence did not differ significantly between the two initiation schedules, but one patient in the rapid initiation group dropped out because of intolerable somnolence. No orthostatic hypotension was reported by any patient in this study, which is consistent with the results of a study of rapid initiation of quetiapine by Hatim et al. [10].

At all time points, the groups did not differ in either the BARS or the SAS score, but the BARS and SAS scores declined significantly from baseline only in the rapid initiation group. This finding is notable because drug-induced EPSs are known to compromise adherence to medication schedules [19]. Some findings in other investigations support the claim that switching to quetiapine reduces pre-existing neuroleptic-induced extrapyramidal side effects, causing, in particular, a significant reduction in Parkinsonism and akathisia [20].

Although no significant intergroup difference in the CGI-S scores and PANSS positive scores was observed, improvements in the CGI-S scores and PANSS positive scores were maintained from the first week until the end of the study only in the rapid initiation group. The PANSS negative score also improved significantly throughout the present study only for the rapid initiation group.

The first limitation of this study is the small sample size and the random assignment of patients in a ratio of 3:1 to rapid and conventional initiation groups, which resulted in low statistical power, which was insufficient to detect differences. The second limitation was the failure to prohibit the use of concomitant psychotropic drugs and sedatives; however, this was not ethically possible because our patients had underlying diseases that required the use of these concomitant medications. In an attempt to control this variable, all concomitant medications were stably dosed for 4 weeks before randomization, and no significant difference in this parameter existed between the two groups. The most common concomitant medication was benzodiazepam. The third limitation was the significant difference between the quetiapine doses of the rapid and conventional initiation groups at Day 14, which may have affected the efficacy data for the two groups at the end of study. Recent investigations have suggested that higher doses of quetiapine have greater therapeutic efficacy [13]. Other limitations were an excessively short washout period and rater bias that was associated with the open trial design.

In conclusion, in a 2-week study of patients with schizophrenia or schizoaffective disorders, a rapid initiation regimen with a higher dose of quetiapine than that conventionally used (up to 800 mg/d by Day 4) was well tolerated with an acceptable safety profile and did not compromise efficacy relative to the conventional initiation regimen.

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